REMARKS

I. Support for the Amendments

Claims 1 and 7-29 are presently in the application. New claims 17-29 have been added.

Support for new claims 17-29 can be found in the original specification. Additional support for new claims 17-29 can be found, e.g., on page 4, lines 5-14; from page 5, line 26, to page 6, line 25; from page 11, line 31, to page 12, line 5; and in the Example and Figures.

II. Status of the Claims

Claims 1-16 were originally in the application, with claim 1 being the independent claim. Previously, claims 1 and 7-16 were in the application.. Claims 2-6 had been canceled.

New claims 17-29 have been added, and claims 1 and 7-29 are presently in the application.

III. The Declaration has Overcome Some of the Previous Rejections

The Examiner has acknowledged that that the Declaration under 37 C.F.R. §1.131 by Mary L. Owens, mailed September 21, 2006, has overcome the previous rejection of claims 1-16 under 35 U.S.C. §102(a) by Shumach et al. (Arch. Dermatol. 38:1165-1171; "Shumach"), as well as that of Geisse et al. (J. Am. Acad. Dermatol. 2002, 47: 390-398;

"Geisse"), used in the previous rejection of claims 1-12 and 15 under 35 U.S.C. §103(a). Applicants thank the Examiner for consideration of the Declaration.

IV. The Rejection of Claims 1, 7-12, and 16 under 35 U.S.C. §103(a) is Traversed

The Examiner has maintained the previous rejection of claims 1, 7-12, and 16, alleging obviousness over Marks et al. (J. Am. Acad. Dermatol. 2001, 44: 807-813; "Marks") or Beutner et al. (J. Am. Acad. Dermatol. 1999, 41: 1002-1007; "Beutner") or Kagy et al. (Dermatol. Surg. 2000, 26: 577-579; "Kagy").

Applicants respectfully disagree and request reconsideration of these rejections accordingly, in light of both the arguments previously asserted and the following.

A. The Rejection over Marks

As noted by the Examiner, Marks describes protocols for treatment of superficial basal cell carcinoma (sBCC) in which 5% imiqimod cream was administered to four groups of patients for six weeks either twice every day, once every day, twice daily three days/week, or once daily three days/week. There is no discussion of the spacing of the treatment days for the two categories in which treatment took place three days/week. **Marks fails to disclose the significance of treatment for five consecutive days followed by two days of rest.**

Moreover, Marks states:

> Sixty of the 99 [total] patients (60.6%) had 100% compliance with the intended dosing schedule. ***Investigators could allow a rest period of up to a week at a time if local skin reactions caused discomfort to the patient***; this reduced the number of applications during the available 6-week treatment period. A total of

> 93 patients (93.9%) had at least 60% of the scheduled applications. Complete (100%) compliance with dosing did not appear necessary to achieve a complete efficacy response.... [P. 809, c. 2 – p. 810, c. 1; all emphasis added.]

The rest periods of Marks were the *result* of the adverse reaction(s) – *not* as a means of *preventing, reducing, or ameliorating* the adverse reaction(s), unlike the present invention.

Table III shows the frequency of application site reactions reported by the patients. In all but one category (itching), the frequency appears to have a relationship to dose with a general decrease in incidence as the dose decreases (see p. 810). Table IV shows the frequency of severe local skin reactions as assessed by the investigators. In most categories (except erosion), there appears to be at least some relationship to dose (see p. 810).

Table II shows the complete response rate by treatment group. Similarly, the response appears to have a relationship to dose with a general decrease in response as the dose decreases (twice every day: 100%; once every day: 87.9%; twice daily for 3 days/week: 73.3%; once daily for 3 days/week: 69.7%) (see p. 809). **In essence, as the dose in Marks decreases, so do the majority of the adverse reactions and the efficacy of the treatment.**

Nothing in Marks describes or suggests the present invention. In the present application, the subjects were treated either once daily for seven days/week for six weeks or once daily for five consecutive days/week with two days of rest for six weeks. (Likewise, there were two placebo groups.) Figure 1 shows the histological assessment, while Figure 2 summarizes the results of the composite assessment as a percentage of subjects having both (a) no clinical evidence of BCC twelve weeks after the end of the treatment, and (b) a complete histological response. (See pages 11-13 and Figures 1-3.) In Figure 1, the group treated seven days/week had a 79% response rate, while the group treated five consecutive days/week had an 82% response rate. In Figure 2, the group treated seven days/week had a

73% response rate, while the group treated five consecutive days/week had a 75% response rate. In contrast, the percentage of patients having a given local skin reaction (erythema, erosion, ulceration, and scabbing/crusting) is greater in the group treated seven days/week. (erythema: 93% [7 days/week] vs. 88% [5 days/week]; erosion: 52% vs. 36%; ulceration: 28% vs. 22%; scabbing/crusting [65% vs. 52%]).

Surprisingly, despite having a lower incidence of local skin reactions, the group treated five consecutive days/week had at least as good a treatment response rate as the group treated seven days/week.

In light of these unexpected results, Applicants respectfully submit that claims 1, 7-12, and 16 are not obvious over Marks.

B. The Rejection over Beutner

As noted by the Examiner, Beutner describes protocols for treatment of basal cell carcinoma (BCC) in which 5% imiqimod cream was administered to five groups of patients either twice daily, once daily, three times weekly, twice weekly, or once weekly. (Additional groups were treated with a placebo.) Patients continued in the study until either two weeks after the target tumor was clinically cleared (as determined by the investigator) or for 16 weeks of treatment. (See p. 1003.) There is no discussion of the spacing of the treatment days for the categories in which treatment took place three times weekly or twice weekly. **Beutner fails to disclose the significance of treatment for five consecutive days followed by two days of rest.**

Moreover, Beutner states:

> Some patients took rest periods, more commonly in dose groups where imiquimod was applied more frequently. ***Rest periods were required by all of***

> ***the twice daily, half of the once daily, and a quarter of the 3 times weekly subjects*** but by none of the other groups (Table III). [P. 1004, c. 2; all emphasis added.]

Beutner fails to describe the types of rest periods taken, however. The fact that they were "required" suggests that the rest periods were the *result* of the adverse reaction(s) – *not* as a means of *preventing, reducing, or ameliorating* the adverse reaction(s).

As shown in Table III, adverse reactions occurred at various rates. (See also pp. 1004-1006.) While a few adverse reactions (e.g., discharge at target site) appear to have a relationship to dose with a general decrease in incidence as the dose decreases, others do not.

As shown in Table II, patients in the twice daily, once daily, and three times weekly groups showed complete clearance of treated BCC (median length of treatment = 10 weeks, 13 weeks, and 14.5 weeks, respectively). (See also pp. 1004-1006.)

Nothing in Beutner describes or suggests the present invention. The present application has been discussed at length, *supra*, and the same comments apply here.

In light of the unexpected results of the present invention, Applicants respectfully submit that claims 1, 7-12, and 16 are not obvious over Beutner.

C. The Rejection over Kagy

As noted by the Examiner, Kagy describes protocols for treatment of basal cell carcinoma (BCC) in which 5% imiqimod cream was administered to a patient once daily for 18 weeks (p. 577, c. 1). It also reported the patient's difficulty in tolerating the treatment for at least one treatment site (p. 578, c. 1).

Also noted by the Examiner, a Commentary by John Geisse, which follows the Kagy case report, states:

> What remains to be defined is the optimal dosing in which there can be three variables: concentration, the frequency of application, and the duration of the course of therapy. At the present time, the concentration of the drug is fixed at 5% by the available formulation. As to frequency of application, our work clearly demonstrated dose-dependent effects particularly in terms of local adverse reactions. In the extreme, with twice daily application under occlusion, we generated ulceration. **With decreasing application, to once daily, five times weekly, three times weekly and once weekly, there was a decline in the local adverse events that we noted.** This was contrary to what we had expected entering the clinical trial. The rapidity at which these reactions began and the severity which they attained is beyond what we had noted in our previous work in treating many patients with genital warts with this cream. Apparently, actinically damaged skin is far more susceptible to the inflammatory properties of this compound, plus the target tumor seems to generate a variably brisk immune response depending upon the patient and unknown variables.
>
> As to the duration of therapy, in our original study, most of the patients were treated for the maximal sixteen weeks so as to not miss the therapeutic effect....Thus, at the present time (as we narrow down the options) it appears as though the optimal duration of therapy is in the range of six to sixteen weeks. [P. 578, cc. 1-2; all emphasis added.]

While Geisse does mention **"five times weekly,"** he discusses it **in reference to "decreasing application" as a stepping stone in the continuum of "frequency of application" between "once daily" and "three times weekly"** with respect to an **apparently concordant "decline" in local adverse events.**

The Examiner maintains that Geisse, whom the Examiner describes as one skilled in the art, concludes:

> ....Topical Imiquimod in our experience can rarely leave hypopigmentation and superficial punctate scarring when used to treat basal cell carcinoma. **These complications are most commonly seen in patients dosed daily or twice daily.** These unusual but remarkable local reactions are the exception and not the rule and are clearly dose-dependent as we have indicated.

> In broad terms, our personal opinion is that the optimal dosing would be five out of seven days per week for a duration of therapy of about twelve weeks. **Patients should be allowed rest periods during treatment if local reactions become symptomatic. Further clinical trials are needed to determine the optimal dosing to minimize cutaneous side-effects and maximize efficacy**.... [P. 579, cc. 1-2; all emphasis added.]

This opinion, however, is based on the earlier statement concerning the continuum of frequency. In essence, Geisse is referring to a frequency on the continuum as a means of avoiding some of the complications with **no mention or suggestion of the number of consecutive days per week**, because **he is only concerned with overall frequency**.

Moreover, **Geisse fails to describe the types of rest periods taken, however. In fact, Geisse specifically states that the rest periods "should be allowed...if local reactions become symptomatic" – i.e., as the *result* of the adverse reaction(s) – *not* as a means of *preventing, reducing, or ameliorating* the adverse reaction(s).**

He makes no mention of a specific protocol in which five consecutive days/week are punctuated by two days of rest.

Both Kagy and Geisse fail to disclose the significance of treatment for five consecutive days followed by two days of rest.

Nothing in Kagy (including the Commentary by Geisse) describes or suggests the present invention. The present application has been discussed at length, *supra*, and the same comments apply here.

In light of the unexpected results of the present invention, Applicants respectfully submit that claims 1, 7-12, and 16 are not obvious over Kagy.

V. The Rejection of Claims 13-15 under 35 U.S.C. §103(a) is Traversed

The Examiner has maintained the previous rejection of claims 13-15, alleging obviousness over Marks et al. (J. Am. Acad. Dermatol. 2001, 44: 807-813; "Marks") or Beutner et al. (J. Am. Acad. Dermatol. 1999, 41: 1002-1007; "Beutner") or Kagy et al. (Dermatol. Surg. 2000, 26: 577-579; "Kagy"), in view of Aldara™ (FDA, Labeling Revision 2001).

Applicants respectfully disagree and request reconsideration of these rejections accordingly, in light of both the arguments previously asserted and the following.

The Examiner has cited the Aldara™ Labeling Revision as teaching that the cream should be applied to the target area prior to normal sleeping hours and left on the skin for 6-10 hours.

Marks, Beutner, and Kagy have been discussed at length, *supra*, and the same arguments apply here. Applicants respectfully submit that the Aldara™ Labeling Revision fails to remedy the deficiencies of Marks, Beutner, and Kagy.

Applicants respectfully submit that claims 13-15 fulfill the requirements of 35 U.S.C. §103(a) and request the Examiner's reconsideration of these claims accordingly.

VI. The Information Disclosure Statement

An Information Disclosure Statement was mailed by previous counsel on August 18, 2004. Japanese Patent Applications 9-208584 (B3), 11-80156 (B4, provided as translation only), and 11-222432 (B5) were not initialed by the Examiner. Applicants are submitting

herewith the three references with abstracts provided by esp@cenet and request consideration of the references and the previously submitted translation accordingly.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

Applicants hereby request a three-month extension of time for the Amendment and accompanying materials. If, however, a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an extension of time and the Commissioner is hereby authorized to charge our deposit account no. 04-1105 for the appropriate fee. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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